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NEXT-GENERATION SEQUENCING (NGS) PROFILING AND CYTOGENETIC ANALYSIS FOR PATIENTS WITH PH-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS

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INTRODUCTION

Determination of driver mutations in *JAK2, CALR* and *MPL* genes is the gold standard in the molecular diagnostics of patients with Ph-negative myeloproliferative neoplasms. However, the genomic landscape of such patients is very wide and standard methods cannot provide a complete picture of the course and prognosis of such patients. The next generation sequencing (NGS) method allows to simultaneously analyze an extensive panel of genes, as well as assess the level of allele burden of identified variant with mutations. This fact makes NGS an important tool in identifying pathogenic mutations and predicting the course of the disease in patients with Ph-MPN. Cytogenetic aberrations are also an important prognostic factors in Ph-MPN. The connection between pathogenic mutations and chromosomal abnormalities is the subject of discussion.

AIM

To assess the role of NGS profiling and cytogenetic analysis in evaluating the prognosis of the disease and the effectiveness of treatment for patients with Ph-negative myeloproliferative neoplasms.

PATIENTS & METHODS

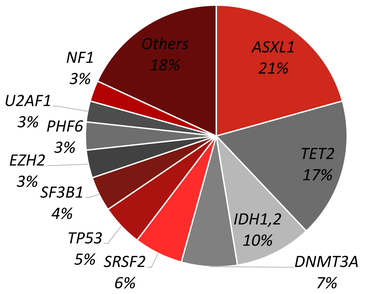
140 patients:
- 55 men and 85 women
- PV (40/140), ET(30/140), PMF (70/140)
- median age - 54 years (IQR 19-85).

NGS:
- Custom panel of 118 genes
- Average reading depth of 1000x on MiSeq
- Limit of 3% variant allele frequency
- Analysis with COSMIC and Franklin databases

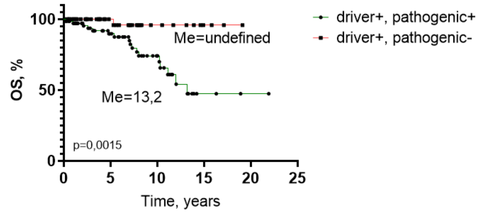
Chromosome analysis:
- fresh bone marrow aspirates
- G-banding with trypsin stain

Statistical analysis:
- the Kaplan-Meier method with statistical significance assessed using the Cox-Mantel and chi-square tests.

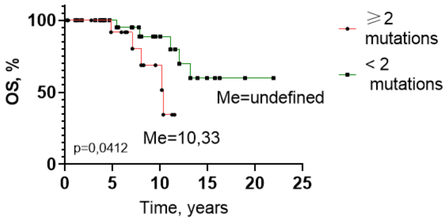
RESULTS



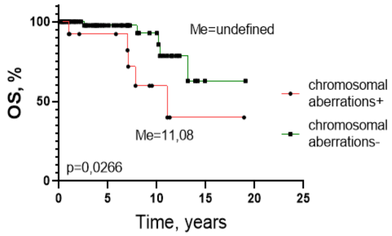
- 71/140 patients (51%) have pathogenic mutations
- Me=1
- In 25 genes



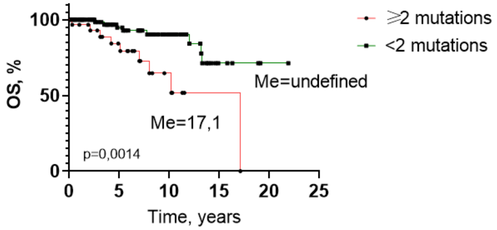
Impact of pathogenic mutations on OS in combination with driver mutations



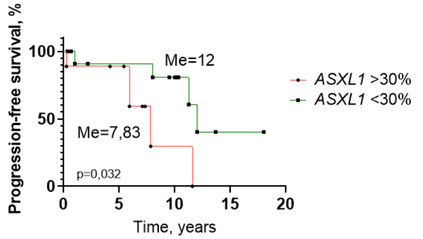
Impact of number of pathogenic mutations on OS of patients treated with Ruxolitinib



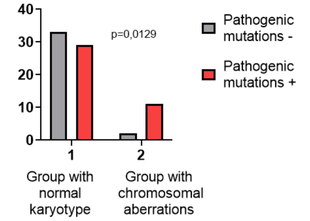
Impact chromosomal abnormalities on OS



Impact of number of pathogenic mutations on OS



Impact of *ASXL1* allele burden on progression-free survival



Pathogenic mutations are more common in patients with chromosomal aberrations

CONCLUSIONS

1. NGS is an effective method that confirms the disease clonality and allows identifying high-risk groups in patients with Ph-MPN
2. Pathogenic mutations are detected in 51% of patients with Ph-MPN
3. Significantly worsening indicators of OS or PFS in Ph-MPN are:
- combination of pathogenic and driver mutations
- 2 or more pathogenic mutations
- additional chromosomal aberrations
- allele burden of *ASXL1* >30%
4. 2 or more pathogenic mutations reduce the effectiveness of Ruxolitinib therapy
5. An integrated approach to the diagnosis of Ph-MPN using all cyto- and molecular genetic technologies allows you to establish a diagnosis, assess the prognostic features of the disease and select the most effective personalized therapy

CONTACT INFORMATION

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